8M

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,453	05/26/2000	Jacques Mallet	03804.0114-02	9203

7590 05/06/2004

FINNEGAN, HENDERSON, FARABOW
GARRETT & DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,453	MALLET ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Appeal brief filed 2-24-2004 has been received.

2. The finality of the office action is hereby withdrawn and a new office action is set forth.

3. Claims 16-26 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

When the claims are analyzed in light of the specification, instant invention encompasses any nucleic acid that encodes any mutated form of p53 which antagonizes wild type p53-mediated neuronal cell degeneration in vitro; (ii) any site for binding of p53 to DNA; and (iii) any nucleic acid that encodes an antisense RNA which inhibits expression of p53. However, the specification discloses only SEQ ID No 1 which is an antisense oligonucleotide to p53. The specification on page 4 (lines 21-27) discloses a p53 mutant (p53Val135) known in the art. The specification also discloses a consensus p53-binding site (SEQ ID NO 2) taught in the art (Funk et al. Molecular and Cellular Biology 1992).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification while describes one species of antisense oligo and one p53 binding site, does not describe

the complete structure of a sufficient number of nucleic acids that encode a mutated form of p53 or a site for p53 binding to any DNA that would antagonize the wild type p53 mediated neuronal cell degeneration. The specification neither teaches complete structure of the representative number of species of the claimed genera nor does it teach any identifying characteristics of the claimed molecules that would be common to all the species of the claimed genera. The specification does not provide any disclosure as to how the sequence structure of one nucleic acid species of the each genus claimed would have been same or different compared to the sequence structure of another species. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only identifying characteristic is that the sequence has antagonizing effect on wild type p53 or is site for p53 binding or inhibits expression of p53 which are putative functions. However, a functional characteristic does not allow differentiation among different species of the claimed genera since any species would have the function.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed genus of nucleic acid, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

3. Claims 16-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) a recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, wherein said recombinant virus comprises a nucleic acid selected from the group consisting of (i) a nucleic acid encoding the p53Val135 mutant of p53; (ii) the site for binding of p53 to DNA wherein said site consists essentially of the sequence of SEQ ID NO 2; and (iii) a nucleic acid encoding an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO 1 and (B) a method of inhibiting glutamate mediated ischemic neuronal cell death in culture by administering the cells with a nucleic acid, which encodes an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO 1, does not reasonably provide enablement for the claimed vectors comprising any nucleic acid encompassed by the claimed invention or for a method for inhibiting toxicity using any nucleic acid encompassed by the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention encompasses Claimed invention encompasses (i) any nucleic acid that encodes any mutated form of p53 which antagonizes wild type p53-mediated neuronal cell degeneration in vitro; (ii) any site for binding of p53 to DNA; (iii) any nucleic acid that encodes an antisense RNA which inhibits expression of p53 and (iv) an active variant of SEQ ID NO 2. Additionally, the invention encompasses inhibiting toxicity in cultured neuronal cells by delivering the claimed nucleic acids to the cells.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

First, the specification is not enabling for the claimed polynucleotides of claims because the specification does not teach how to make a polynucleotide that encodes a mutant of p53 that would antagonize the wild type p53 mediated neuronal cell degeneration. The specification on page 7, lines 13-21 makes a general statement which reiterates what is recited in instantly presented claims. On page 4, lines 17-28, the specification lists a p53Val135 mutant and that the mutant may be a negative dominant mutant of p53 consisting essentially of inactive mutated form which competes with the wild type protein for binding to DNA. The specification, however, does not provide any guidance to make such a dominant negative mutant or any mutant of p53, what parts of the protein were to be mutated or altered in order to get a mutant that would meet the functional requirements claimed. Regarding the p53Val135, the specification does not provide any evidence whether this mutant would have antagonized the wild type mediated p53 mediated neuronal cell degeneration. While the art of record (Moberg et al Journal of Cellular Biochemistry 49:208-215, 1992 or Michalovitz et al Cell 62: 671-680, 1990) disclose that the p53Val135 is a temperature sensitive mutant of p53 which is transforming at one temperature, these arts do not teach or provide any guidance or evidence that the protein antagonizes the function of wild type p53. The arts do not teach what mutant will be able to antagonize the neuronal cell

degenerative effects of p53. As for the specification, it does not provide any evidence either that p53 caused neuronal cell degeneration and that this mutant of p53 or any other mutant of p53 could antagonize such effects of p53 on neuronal cell. It is noted that the specification in example 1 teaches that a p53 knockout mouse showed a higher mean volume of infarct compared to a control mouse (see the table on page 15). However, these results in no way indicate that p53 is responsible for neuronal cell death in the knockout mouse. While the art of record (Chopp et al. Biochemical and Biophysical Research Communications, 1992) teaches association of increased expression of p53 with ischemic parts of brain, neither the specification nor the art of record teaches that any mutant of p53 could inhibit any toxicity in neuronal cell culture. In summary, neither the art of record or the specification as filed teaches how to make and use a mutant p53 that would have a function as recited.

The specification does not teach what parts or amino acids of p53 protein could be mutated to obtain a protein that would antagonize the wild type activity for inhibiting neuronal cell death. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other

characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity of the protein of interest. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol. 247, pp. 1306-1310, especially p. 1306, column 2, paragraph 2; and see Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merzer (ed.), pages 433&492-495). Applicant has provided little or no guidance beyond the mere general statements to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which could be mutated or altered so as to make a mutant protein that would have antagonized the neuronal cell degeneration effects of wild type p53.

Regarding the sequence of the site for DNA binding (and variants thereof) and antisense RNA encoding nucleic acids, the specification discloses a consensus p53 binding domain (SEQ ID NO 2) taught in the art (Funk et al. Molecular and Cellular Biology 1992) and an antisense oligonucleotide sequence (SEQ ID NO 1). Except for these two sequences, the specification does not provide any specific guidance how to make any other p53 DNA binding domain or a variant of such a sequence or any other antisense nucleic acid. Again, except for mere general statements in the specification (such as on page 4 of the specification), the specification does not provide any specific teaching as to how to make such DNA binding sites (variants of these) or antisense RNA encoding nucleic acids. On page 4, applicants list certain WO documents, however, none of these arts teach how to make the claimed nucleic acid that would have the function as claimed.
While it would have been routine to make mutants, it was not routine in the art to make random mutations in a given nucleic acids to produce mutants or variants. It would have required undue experimentation to produce mutants or variants as encompassed by the claimed invention because neither the specification nor the art of record provides any specific guidance as to what parts of the nucleic acid to alter such as to produce nucleic acid that would have desired function and this was not routine in the art.

Regarding the nucleic acid encoding an antisense RNA, at the time of the invention, the art of designing antisense oligonucleotides for inhibiting gene

expression was unpredictable. For example, Sherman (Annals of NY Acad. Sci. 616:201-204, 1990), discussed some of the limitations and potential problems associated with antisense targeted gene expression inhibition. For example, antisense sequences directed against different regions of a target nucleic acid would be differentially active, such as the antisense sequences that hybridize with the 5' end of a mRNA would have different levels of effects on the expression of the targeted gene, compared to sequences targeting the internal regions of the mRNA because they would target different steps of gene expression. These factors are further compounded by the fact that base compositions as well as tertiary structure of the target sequence will determine the accessibility of the target sequence to the antisense sequence. Additionally, in order to be maximally effective, the antisense molecules must reach their respective intracellular target in an intact state. In another review, Rojanasakul (Advanced Drug Delivery Reviews 18:115-131, 1996) analyzed the issue: can antisense work in living system and discusses issues such as, how can antisense oligonucleotides be targeted to diseases cells, sparing normal cells and many instances one would see more effect on gene expression with a control oligo than the target oligo. Another issue is their degradation and effects of the degradation products on gene expression and cellular metabolism. It is noted that the specification neither provides any specific guidance to make antisense oligonucleotides nor does it teach as to how an artisan of skill would have addressed art recognized limitations associated with antisense oligonucleotide design and usage for inhibition of gene expression. An artisan of skill would have required undue experimentation of make the claimed antisense nucleic acid because the art was not routine and was unpredictable at the time of the specification.

In conclusion, the specification as filed does not provide sufficient guidance for an artisan of skill to have practiced the claimed invention commensurate with the full scope of the claims and therefore, limiting the scope of the claimed invention to (A) a recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, wherein said recombinant virus comprises a nucleic acid selected from the group consisting of (i) a nucleic

acid encoding the p53Val135 mutant of p53; (ii) the site for binding of p53 to DNA wherein said site consists essentially of the sequence of SEQ ID NO 2; (iii) a nucleic acid encoding an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO 1 and (B) a method of inhibiting glutamate mediated ischemic neuronal cell death in culture by administering the cells with a nucleic acid encodes an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO 1 is proper.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 16, 17, 19, 20, 21, 22, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michalovitz et al (Cell 62: 671-680, 1990) in view of Moberg et al (Journal of Cellular Biochemistry 49:208-215, 1992), La Gal La Salle (Science 259: 988-990, 1993) and Chopp et al (Biochemical and Biophysical Research Communications, 1992).

The claimed invention is drawn a recombinant virus comprising a nucleic acid encoding a mutant P53 protein, wherein the virus is selected from the group of an adenovirus, a herpes virus, and a adeno-associated virus, the nucleic acid is p53Val135 mutant, a method of inhibiting toxicity in cultured neuronal cells and wherein the vector nucleic acid is in a vector and the vector is a replication defective virus.

At the time of the invention, Michalovitz et al taught the transfection of rat embryo fibroblasts with an expression vector encoding the p53Val135 mutant and that the mutant is a temperature sensitive mutant whose expression can be

modulated by changing the temperature of the culture medium cells are grown (see the abstract, figure 1, table 1 and rest of the article). They further taught that this mutant suppresses oncogene-mediated transformation of the cells at 32.5 celcius, which showed that this mutant could function as wild type p53 (see the last paragraph in the left column on page 673 continued in the right) column. On the other hand this mutant functions as a mutant p53 in transforming cells in the presence of oncogenes at high temperature (the discussion on page 677). This art also teaches that a ts mutant of p53 would provide major clues toward understanding the mode of action of the protein (see last paragraph in left column on page 672). Micahlovitz et al does not teach a viral vector that comprises mutant p53 that antagonized the neuronal cell degeneration in vitro mediated by wild type p53. It is noted that while the art of Michalovitz et al does not teach inhibition of neuronal cell degeneration by a mutant p53, the art teaches the same p53 mutant which is recited in claim 21.

Chopp et al (Biochemical and Biophysical Research Communications, 1992), while studying the association of p53 with the 72 kDa heat shock protein and role of heat shock protein in cerebral ischemia, reported that p53 was expressed in regions of severe ischemic cell damage and that p53 presence was associated with neuronal necrosis (page 1203, first full paragraph and the last paragraph on page 1207).

Moberg et al taught that p53 repressed transcription of murine c-myc promoter in a human glial cell and that the mutant p53 did not suppress transcription of c-myc promoter (see the abstract).

Salle et al taught a replication defective adenoviral vector for gene transfer into neurons and into glia in the brain. They further taught that adenoviral vectors could be used for transferring gene in brain both in vitro and in vivo (see the first paragraph in left column on page 988) and that adenoviral vectors have several advantages for gene transfer, such as they can accommodate large inserts, have a larger host range, and low pathogenicity in humans and high titers could be produced.

It would have been obvious to an artisan of ordinary skill to make an adenoviral vector comprising a nucleic acid encoding a mutant p53, p53Val135, by

cloning the nucleic acid sequence of Michalovitz et al in the vector of Salle et al and expressing the vector in a glial cell or neuronal cell with a reasonable expectation of success. An artisan of skill would have been motivated to make such an adenoviral vector because the results of Michalovitz et al that p53Val135 behaved both as a wild type and a mutant p53 protein under different conditions and the results of Moberg et al that mutant p53 did not suppress c-myc promoter indicated different effects of mutant p53 and an artisan of skill would have been able to test the activity of the both wild type as well as mutant p53 using the same construct. An artisan would have been motivated to use adenoviral vector because Salle et al teach that it has advantages over other vector for both in vitro and in vivo use. Regarding claims 25 and 26, it is noted that it would have been obvious to use the adenoviral vector comprising p53Val135 in identifying compounds that modify transformation induced by c-myc in the glial or neuronal cells because of the temperature sensitive phenotype of the p53Val135 mutant.

8. Claims 16-23, 25, 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levrero et al. taken with Michalovitz et al. Funk et al., and Chopp et al.

Levrero et al. (Gene, 1991) disclose a recombinant virus, specifically, a defective adenovirus for the purpose of harboring foreign nucleic acids in vitro and in vivo. The recombinant virus taught by Levrero et al. differs from the claimed recombinant virus in that the nucleic acids inserted into the recombinant adenovirus consist of the hepatitis B (HB) virus *s* gene or the CAT (chloramphenicol acetyltransferase) gene rather than nucleic acids from the group consisting of (a) nucleic acids encoding mutated p53 antagonists; (b) a p53 DNA binding site; and (c) nucleic acids encoding antisense RNA which inhibits p53 expression.

However, at the time the claimed invention was made, Michalovitz et al. (Journal of Cellular Biochemistry, 1991) disclosed mutated forms of various mouse p53 DNA clones (see Fig. 1, page 23) and reveals the ability of a mutant p53 to

interfere with the function of *wt* p53 (page 25, column 2, 2nd paragraph). Funk et al. (Molecular and Cellular Biology, 1992) disclosed a specific DNA binding site for p53 identical to that of Sequence ID No. 2 (page 2866, abstract). The application of these nucleic acids to p53 expression is relevant due to the association of p53 with severe ischemic cell damage disclosed by Chopp et al. (Biochemical and Biophysical Research Communications, 1992). Chopp et al. disclose data suggesting that induction of p53 may play a role in promoting cell death (page 1207, last paragraph). Therefore, the use of nucleic acids as disclosed by Michalovitz et al. and Funk et al. would interfere or block p53 activity and thus suppress p53 expression in cells such as neurons found in ischemic tissue. It is emphasized that at the time of the invention, it was routine in the art to make different viral vectors such as HERPES vector or adeno-associated viral vectors for infecting mammalian cells (eg. see the abstract of Geller J. Neurosci Methods 36:91-103, 1991 for HSV-1 vectors that were used for transducing neural cells; see abstract of Carter BJ. Curr. Opin Biotechnology. 3:533-539, 1992 for review of adeno-associated virus vectors).

Accordingly, in view of the teachings of Michalovitz et al., Funk et al., and Chopp et al., it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the recombinant virus taught by Levrero et al. by inserting nucleic acid encoding mutant p53Val135 or DNA of Funk et al for the expected effect of suppressing p53 activity. An artisan would have had reasonable expectation of success because the all the relevant methods and techniques have been taught by the arts. An artisan of skill would have been motivated to use an adenoviral vector because such a vector was shown to be efficient in transfecting neuronal cells. Additionally, an artisan of skill would have been motivated to make HERPES or adeno-associated vectors to design the best vector. Thus, Applicant's claimed invention as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

9. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith taken with Soussi et al., and further in view of Chopp et al.

Smith (US Patent 5,087,617) discloses a method of inhibiting p53 expression in vitro and in vivo by administering nucleic acids encoding nucleic acids capable of blocking the mRNA transcribed from the p53 gene (column 5, lines 33-37). Smith differs from the claimed method in that the p53 antisense oligonucleotide does not have an identical sequence to that disclosed in Sequence ID No. 1. Also, Smith differs from the claimed method in that the target cells are cancerous cells of the hematopoietic system rather than neuronal cells.

However, at the time the claimed invention was made, Soussi et al. (Nucleic Acids Research, 1988) disclose a sequence identical to that of Sequence ID No. 1. The application of this nucleic acid to p53 expression is relevant due to the association of p53 with severe ischemic neuronal cell damage disclosed by Chopp et al. (Biochemical and Biophysical Research Communications, 1992). Chopp et al. disclose data suggesting that induction of p53 may play a role in promoting neuronal cell death (page 1207, last paragraph). Therefore, the use of nucleic acid as disclosed by Soussi et al. would interfere or block p53 activity and thus suppress p53 expression in cells such as neurons found in ischemic tissue.

Accordingly, in view of the teachings of Soussi et al. and Chopp et al., it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the method of Smith by administering a p53 antisense oligonucleotide for the expected effect of suppressing p53 activity by inhibition. Thus, Applicant's claimed invention as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

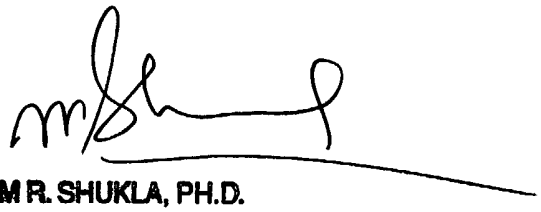
4. Applicant's arguments with respect to claims 16-26 have been considered but are moot in view of the new ground(s) of rejection.

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (571) 272-0548.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER